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ABSTRACT

Introduction The ERAS protocol (Enhanced Recovery After Surgery) is a multimodal pathway aimed to reduce surgical stress and to allow a rapid postoperative recovery. Application of the ERAS protocol to colorectal cancer surgery has been limited to a minority of hospitals in Italy. To promote the systematic adoption of ERAS in the entire regional hospital network in Piemonte an Audit and Feedback approach (A&F) has been adopted together with a cluster randomised trial to estimate the true impact of the protocol on a large, unselected population.

Methods A multicentre stepped wedge cluster randomised trial is designed for comparison between standard perioperative management and the management according to the ERAS protocol. The primary outcome is the length of hospital stay (LOS). Secondary outcomes are: incidence of postoperative complications, time to patients’ recovery, control of pain and patients’ satisfaction. With an A&F approach the adherence to the ERAS items is monitored through a dedicated area in the study web site. The study includes 28 surgical centres, stratified by activity volume and randomly divided into four groups. Each group is randomly assigned to a different activation period of the ERAS protocol. There are four activation periods, each over 3 months. However, the planned calendar and the total duration of the study have been extended by 6 months due to the COVID-19 pandemic. The expected sample size of about 2200 patients has a high statistical power (88%) to detect a reduction of LOS of 1 day and to estimate clinically meaningful changes in the other endpoints.

Ethics and dissemination The study protocol has been approved by the Ethical Committee of the coordinating centre and by all participating centres. Study results will be timely circulated within the hospital network and published in peer-reviewed journals.

Strengths and limitations of this study

- Systematic implementation of the Enhanced Recovery After Surgery (ERAS) protocol in an entire regional network of surgical centres.
- Use of a cluster stepped wedge design to achieve, by the end of the study, the adoption of the ERAS protocol in all the participating centres, followed by an unbiased assessment of the effectiveness of change in clinical practice.
- Development of a comprehensive Audit and Feedback strategy to monitor and encourage adoption of the full ERAS protocol.
- Ability to analyse barriers and facilitators to ERAS protocol implementation at both patient and organisational levels.
- COVID-19 pandemic may limit the hospital ability to reorganise according to the ERAS protocol and complicate the interpretation of the study results.

Trial registration number NCT04037787.

INTRODUCTION

The ERAS protocol (Enhanced Recovery After Surgery) is a multimodal pathway aimed to reduce surgical stress, trying to maintain body homeostasis and to allow a rapid postoperative recovery of the patient undergoing major surgery. 1, 2 The main targets of the ERAS protocol are: to optimise the perioperative management using procedures based on scientific evidence; to favour a better recovery of the patient’s autonomy in the postoperative period; to favour a reduction in length-of-stay...
An Audit and Feedback (A&F) system to verify a team dedicated to training operators and to increase shown a significant reduction in healthcare costs. Studies conducted in Alberta, following a national adoption of the ERAS pathway in colorectal surgery, have also shown a significant reduction in healthcare costs.

A formal programme for the implementation of the ERAS protocol requires three elements:

- An updated and shared ERAS operating protocol.
- A team dedicated to training operators and to increase compliance with the protocol.
- An Audit and Feedback (A&F) system to verify compliance with the protocol and to monitor clinical outcomes.

In Italy the PeriOperative Italian Society (POIS, http://perioperativeitaliansociety.org) aims to disseminate the ERAS strategy because its mission is to promote the minimally invasive surgical procedures and improve the patient’s quality of life in the perioperative period. The POIS has activated a network of over 70 Italian hospitals and has developed a database for colorectal surgery which has allowed the recent publication of multicentre studies. Although the ERAS protocol has been known for some time, its application has been limited to a minority of hospitals, at least in Piemonte (a region of North West of Italy with 4.3 million population). To promote the systematic adoption of ERAS in the entire regional hospital network in Piemonte an A&F approach has been adopted together with a cluster randomised controlled study to estimate the true impact of the protocol on a large, unselected population: the ERAS Colon-Rectum Piemonte study. The A&F strategy is recommended by the ERAS Society guidelines for colorectal cancer (quality of evidence: high; recommendation: strong) as an instrument to be applied regularly by healthcare providers when driving change or implementing ERAS programmes.

The project was based on two main hypotheses: (a) the ERAS protocol has a high probability, based on the available evidence, of introducing procedures into clinical practice with a favourable balance between benefits and risks (both for patients and for staff); (b) the diffusion of the protocol only in selected hospitals, particularly open to change, would have a limited impact on the overall quality of the intervention on a regional scale, with an increase in the heterogeneity of services between centres and inequalities among patients.

This regional project is part of a larger project on the evaluation of effectiveness of A&F interventions (EASY-NET), a Network Project funded by the Ministry of Health and the participating Regions (NET:2016-02364191).

METHODS

Trial design

The ERAS Protocol implementation in Piemonte Region for Colorectal Cancer Surgery (ERAS Colon-Rectum Piemonte) (http://www.clinicaltrials.gov) is a prospective multicentre cluster randomised controlled study, with a stepped wedge design, for comparison between standard perioperative management (usual care) and the management according to the ERAS protocol. We hypothesise that the adoption of the protocol will result in a reduction in LOS, complications, healthcare costs and in improvement of functional recovery and patient satisfaction.

Clusters are represented by the general surgery units of the regional hospitals with progressive adoption of the protocol by groups of units, randomly identified according to a specific calendar. At the end of the study, each cluster will have a period of activity according to standard care (‘control period’) and one period of protocol-based practice (‘experimental period’) with a cross-over like design, but with a single transition (from control to experimental).

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist is provided in online supplemental material. Figure 1 shows the study diagram according to the SPIRIT statement.

The manuscript has been prepared according to the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) checklist (online supplemental material), the standardised framework for designing and reporting ERAS-related studies proposed by the ERAS and ERAS USA societies.

### Randomisation

<table>
<thead>
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<th>Group</th>
<th>Baseline</th>
<th>Study period (months)</th>
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<tr>
<td>Group 4</td>
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</table>

Number of patients by period:
- Control patients: 448
- Experimental patients: 0

Experimental period

**Figure 1** Diagram of the Enhanced Recovery After Surgery colon-rectum Piemonte study. Due to COVID-19 outbreak the third period has been extended for three months (lasting 6 rather than 3 months) and the further study periods shifted 3 months forward.
Patients with high complexity or clinical severity, to
►
Patients requiring an urgent surgical procedure.

Units with less than 30 cases per year of colorectal
►
All patients undergoing elective colorectal resection
►
All general surgery units of Piemonte Region hospi-


Inclusion criteria
► All general surgery units of Piemonte Region hospi-
tals that have at least 30 surgical colorectal cancer
cases per year.
► All patients undergoing elective colorectal resection
for malignancy, with or without protective stoma, and
both by minimally invasive or laparotomic approach.

Exclusion criteria
► Units with less than 30 cases per year of colorectal
rectal surgery.
► Patients requiring an urgent surgical procedure.
► Patients with high complexity or clinical severity, to
be documented at the time of admission (e.g., patients
with American Society of Anesthesiologists (ASA)
physical status classification system V).

Stratification and randomisation of the centres
Ahead of the study starting date, all general surgery
units were contacted to assess the level of knowledge
of the ERAS protocol for colorectal surgery. Those centres
that had already fully adopted the protocol before the
start of the study were excluded from randomisation
and included in an observational group. All the other
centres were stratified by the volume of colorectal
interventions performed during 2017 and randomly
divided into four groups, with a similar number of
units and procedures. Then, the four groups were
randomly ordered to activate the protocol according to
a predefined calendar with 3 months interval between
subsequent rounds. This stratified randomisation was
adopted to assure a more homogeneous composition of
the groups in each activation period. All randomisation
procedures were performed by the Clinical Epidemi-
ology unit after anonymising the centres. The calendar
date for protocol activation was communicated to each
group about 2 months before the starting date to allow
sufficient time for the training of the local ERAS team
and to organise the activity.

The centres of the first group started with the protocol
activation after a 3 months period of baseline, during
which only standard care was supplied to the enrolled
patients.

Interventions
ERAS group
In the quarter preceding the date of randomisation,
each group receive specific training on the ERAS prin-
ciples. Training is provided to a selected group of profes-
sionals (surgeons, anaesthetists, nurses and dieticians)
and consists of a 1-day interactive course run by expert
POIS trainers. The selected participants are required to
cascade training to their colleagues at local level. Slides
are shared for this purpose as well as support is offered by
the expert POIS trainers, if required.

Each centre is asked to identify an ‘ERAS team’, which
should include at least one person per professional role,
with the aim of providing support for the local imple-
mentation of the protocol and to be the reference for the
centre.

Control group
Each centre belongs to the control group during the
3 months of baseline and thereafter, until the randomisa-
tion date. During the control period centres are required
to continue with their usual perioperative care and to fill
the Case Report Form (CRF) for the enrolled patients.

Audit and Feedback
The study has a dedicated website (EPICLIN: https://
new.epiclin.it/it/eras_colonretto/) for data entry, moni-
toring and feedback.

From the beginning of the study, all centres can
access the ‘monitoring area’ on Epiclin to keep track of
data collection progress and visualise graph and tables
describing: number of enrolled patients and expected
number in the same period according to cases treated in
the previous year, number of patients keen to participate
to an interview after discharge and number of patients
filling the quality of recovery questionnaire.

Once each group of centres enters the experimental
period, its ERAS team has the opportunity to access a
feedback area. This area displays various graphs moni-
toring the indicators of adherence to all the ERAS
items reported in online supplemental material table
S1. The aim is to verify the centres progress in applying
the protocol in order to promptly identify critical issues
and address them with corrective actions. Each indicator
of adherence is stratified by study period (control and
experimental) to appreciate changes in clinical prac-
tice. A radar graph allows to compare the adherence
of groups of indicators measured in three different situa-
tions: before randomisation, after randomisation and in
a benchmark setting (a small group of regional hospitals
already applying ERAS before the study).

Two months before the ERAS adoption, the regional
coordinating group organises a workshop for each of
the four groups with the expert POIS trainers and the
coordinating/data management team to discuss the feed-
back indicators, the critical issues encountered and find
possible solutions.
A newsletter is sent every 2 months to all the ERAS teams to maintain engagement and motivation in the overall project and to share information on study progress and relevant news.

**Primary outcome**
- Mean LOS, calculated after excluding lengths exceeding a predefined threshold, corresponding to the 94th percentile of the distribution.

**Secondary outcome**
- Percentage of hospital stays exceeding a threshold (≥12 days)
- Postoperative quality of recovery score, measured with the QoR-15 questionnaire around 48 hours after surgery
- Incidence of postsurgical complications, defined according to the Clavien-Dindo classification
- Intensive care unit access in the postoperative period
- Percentage of emergency department (ED) admissions up to 30 days after surgery (regardless of diagnosis)
- Percentage of readmissions to hospital within 30 days after surgery (regardless of diagnosis)
- Percentage of reintervention (within 30 days after surgery).
- Perceived patient satisfaction score measured with the SSQ-8 questionnaire via telephone interview around 2 weeks after discharge (only in a random subsample of patients keen to participate)
- Average healthcare costs, calculated from prehospitalisation up to 30 days after surgery
- Assessment of professionals’ satisfaction, measured qualitatively.

**Data collection**
The CRF is available in a dedicated area of the EPICLIN electronic platform, developed and managed by the Clinical Epidemiology Unit, compliant with all the security requirements of the General Data Protection Regulation (EU regulation 2016/679). Data related to the perioperative care are collected in the database prospectively and uniformly between study periods. Patients are enrolled and sign a consent form after receiving comprehensive oral and written information on the study aims and on the data treatment by the enrolling centre.

The postoperative recovery is measured at 48 hours after surgery through the QoR-15 questionnaire (available and validated in English). Patients’ satisfaction is measured through the SSQ-8 questionnaire (available and validated in English), administered by telephone to a sample of patients or alternatively their caregivers 2 weeks after discharge, by trained personnel.

Professionals’ satisfaction will be qualitatively assessed at the end of the study through questionnaires and focus groups.

Healthcare costs incurred between the first preadmission visit and 30 days after hospital discharge will be evaluated by including the following categories of resources: preintervention visits, hospital stay days (including intensive care days), type of intervention, treatment of complications, reinterventions, ED access, new hospitalisations.

**Patient and public involvement**
No patient involved.

**Statistical plan**
Expected sample size is calculated according to the available data on volume of colorectal cancer surgical cases in Piemonte Region in 2018. The total number of centres meeting the inclusion criteria of at least 30 surgical colorectal cancer cases per year is 28, with an average of approximately 64 interventions/year (1790 expected cases in 1 year). With a randomisation calendar including 7 centres every quarter, 4 periods (15 months in total, including the 3 months at baseline, before the first randomisation) are needed to complete the implementation of the ERAS protocol in all the enrolled centres. Figure 1 describes the sequence of randomisations of the clusters with the number of centres and patients for the control and experimental periods. The total number of cases expected in 15 months is 2240 patients (around 1120 cases in the control period and 1120 in the experimental period). The statistical power of the study is calculated for both the main endpoint (LOS), and for the dichotomous secondary endpoints, according to the sample size and the study design, applying the Hemming and Girling method with STATA software (V.13).

The power is calculated assuming that the application of the protocol entails a reduction in the average LOS (calculated after excluding LOS ≥22 days, corresponding to the 94th percentile) of at least 1 day (from 9.0 to 8.0), which in relation to the standard deviation (3.7) represents an effect size of about 0.27.

The parameters used for the calculation are: mean hospital stay (standard): 9.0 days (standard deviation (SD): 3.7); mean hospital stay (experimental): ≤8.0 days (SD 3.7); alpha error (two tails): 0.05; correlation coefficient within clusters: 0.20; average clusters sample size in each step: 16; number of randomised clusters per step: 7; number of steps (excluding the baseline): 4. Total number of cases (2240) has a statistical power of 0.98.

The statistical power of the study is also calculated to highlight as statistically significant absolute differences of at least 10% of the secondary endpoints measurable as percentages (eg, adherence to the ERAS protocol, complications, reinterventions, etc.). Assuming a reference value of 0.5 (the most unfavourable from a statistical point of view), and keeping all the previous parameters the same, the study has a power of 0.84.

The average LOS (calculated excluding the durations greater than the threshold) will be compared between the two study periods using a random-effect linear regression models, adjusting for the study period and the surgical technique (laparoscopic vs open surgery). The centre will be included in the model as a random effect. For dichotomous endpoints measured as proportions (eg, LOS above the threshold, complications, readmissions), the effect of
implementing the ERAS protocol will be estimated with logistic regression models with random effects, including in the model the same set of covariates used for the analysis of the LOS.

The main analysis will be stratified by characteristics of the centres (classified by volume of activity, degree of adherence to the ERAS protocol at the baseline and other structural characteristics) and by patients’ characteristics. Centres with high adherence to the ERAS protocol at the baseline will be excluded from the main analysis.

To reduce the risk of bias due to patient selection (selection bias, assessed on the basis of the percentage of cases included on the total discharge records in the same enrolment period), analyses will be stratified for completeness of enrolment (with the possibility of excluding centres with greater incompleteness).

To take into account the transition period in each centre, a sensitivity analysis is planned which will exclude the first month of each implementation period of the ERAS protocol. The adoption of the ERAS protocol will also be analysed on the basis of the time elapsed since its introduction, to evaluate the achievement curve of an acceptable and optimal level of application.

In addition, it is expected to evaluate the effect of the ERAS implementation analysing the time trend of the average LOS detectable through the regional hospital discharge records in the 5 years preceding the activation of the ERAS protocol and in the following years, through an interrupted time series analysis.

**Ethics and dissemination**

The study protocol has been approved by the Ethical Committee of the coordinating centre and by all participating centres. The study is conducted under the regulations of the Declaration of Helsinki.

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely at the Clinical Epidemiology Unit, accordingly to all aspects of GDPR 2018. The trial staff at the participating centres will be responsible for ensuring that any data or documentation sent to the Clinical Epidemiology Unit is appropriately anonymised. At the end of the trial, data will be securely archived for a minimum of 20 years.

Study results will be timely circulated within the hospital network and published in peer-reviewed journals, reported in line with the literature Consolidated Standards of Reporting Trials guidelines.

**Trial status**

The trial is currently adhering to V.2.0 of the protocol (approved in January 2020 n.28–2020). Enrolment was initiated 1 September 2019. Recruitment initially expected to be completed in November 2020, due to COVID-19 outbreak is now expected to be completed in May 2021 (6 months delay of the study timetable). At the end of April 2021, the number of patients enrolled is around 2500, 50% of which managed according to standard practice.

**DISCUSSION**

This paper presents the study protocol of a stepped wedge cluster randomised trial aimed to estimate the impact of a quality improvement intervention (the adoption of the ERAS protocol for colorectal cancer surgery) in the entire regional hospital network in Piemonte. In 2018 only few selected hospitals were compliant with the ERAS protocol despite it was published several years before. Among the reasons for this limited diffusion there is the need for a multiprofessional and multidisciplinary management of the patient path besides the requirement to adopt all the items of the protocol. To overcome the usual barriers to innovation in healthcare, especially at the organisation level, and to monitor the changes in terms of appropriateness and safety, a structured A&F strategy has been planned in parallel to the trial. Even if the use of A&F is strongly recommended within the ERAS protocol, it is unusual that this aspect is carefully designed and conducted according to the best practice guidelines.

The chosen study design, a stepped-wedge cluster randomised trial, has several advantages and some limits. Randomisation at patient level would not be feasible due to the organisational nature of the intervention requiring a modification of the care process at centre level. However, compared with other study designs such as a before-after cluster randomised trial, the stepped wedge has a lower risk of bias due to possible confounding time effect and a complete coverage of the participating centres at the end of the study. This last advantage could, at least in theory, also represents a risk in the unlikely, but not impossible, scenario of a detrimental impact of the experimental intervention.

In case of low or partial compliance by participating centres with the ERAS protocol, the effectiveness of A&F should be interpreted considering the disruptive COVID-19 pandemic impact on hospital activity. Anyway, there will be the chance to carefully analyse obstacles and facilitators of the application of the ERAS approach at both patient and organisational levels.

In conclusion, the main interest of the study results lies in the possibility to demonstrate that positive clinical outcomes for the application of ERAS protocol can be obtained not only when it is implemented in selected and highly motivated centres, but also when implemented in a regional network of surgical centres, supported by a careful A&F strategy used to improve compliance. For this last aspect the study will contribute useful evidence to the on-going EASY-NET project (http://easy-net.info/).

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Contributors

Supplemental material

The content of this study has been approved by the relevant ethics committees. All patients gave informed consent for the procedures. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. All authors have approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Eva Pagano http://orcid.org/0000-0001-7552-2901

REFERENCES

Table S1. ERAS protocol items for colorectal cancer surgery.

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<th>ERAS protocol items for colorectal cancer surgery</th>
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<td><strong>Preoperative items</strong></td>
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<tr>
<td>• Preadmission counselling</td>
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<td>• No prolonged fasting</td>
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<tr>
<td>• Carbohydrate loading (maltodextrins administered 3 hours before surgery)</td>
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<tr>
<td>• Immunonutrition in malnourished patients</td>
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<td>• Bowel preparation only for selected cases (surgery of the middle-lower rectum)</td>
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<td>• Thromboembolism prophylaxis</td>
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<td>• Antibiotic prophylaxis</td>
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<td>• No premedication</td>
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<tr>
<td><strong>Intraoperative items</strong></td>
</tr>
<tr>
<td>• Prevention of hypothermia (body warmer/warm intravenous fluids)</td>
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<tr>
<td>• Adoption of minimally invasive surgical techniques (laparoscopic approach is preferable)</td>
</tr>
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<td>• Surgical drainage only in selected cases</td>
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<tr>
<td><strong>Postoperative items</strong></td>
</tr>
<tr>
<td>• Multimodal analgesia (minimized opioid use)</td>
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<tr>
<td>• Prevention of nausea and vomiting</td>
</tr>
<tr>
<td>• No nasogastric tubes</td>
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<tr>
<td>• Early removal of urinary catheter</td>
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<tr>
<td>• Early re-feeding</td>
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<td>• Early mobilization</td>
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<tr>
<td>• Stimulation of gut motility</td>
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<td>• Feedback about compliance and outcomes</td>
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### SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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<th>ItemNo</th>
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<td>All items from the World Health Organization Trial Registration Data Set</td>
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<td>Names, affiliations, and roles of protocol contributors</td>
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<td>Name and contact information for the trial sponsor</td>
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<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
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<td>Introduction</td>
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<td>Background and rationale</td>
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<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
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<td>6b</td>
<td>Explanation for choice of comparators</td>
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<td>Objectives</td>
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<td>Specific objectives or hypotheses</td>
<td>5, line 1</td>
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*SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials*
Trial design

Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting

Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria

Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions

Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes

Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment

Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:
<table>
<thead>
<tr>
<th>Section</th>
<th>Subsection</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>16a</td>
<td>Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.</td>
<td>9, line 21</td>
</tr>
<tr>
<td>Allocation concealment mechanism</td>
<td>16b</td>
<td>Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
<td>NA</td>
</tr>
<tr>
<td>Implementation</td>
<td>16c</td>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</td>
<td>NA</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>17a</td>
<td>Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>17b</td>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
<td>NA</td>
</tr>
<tr>
<td>Methods: Data collection, management, and analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data collection methods</td>
<td>18a</td>
<td>Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.</td>
<td>8, line 29</td>
</tr>
<tr>
<td></td>
<td>18b</td>
<td>Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.</td>
<td>NA</td>
</tr>
<tr>
<td>Data management</td>
<td>19</td>
<td>Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.</td>
<td>NR</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>20a</td>
<td>Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.</td>
<td>9, line 27</td>
</tr>
<tr>
<td></td>
<td>20b</td>
<td>Methods for any additional analyses (e.g., subgroup and adjusted analyses).</td>
<td>10, line 20-31</td>
</tr>
<tr>
<td></td>
<td>20c</td>
<td>Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation).</td>
<td>10, line 24 Missing data NR</td>
</tr>
</tbody>
</table>
### Methods: Monitoring

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data monitoring</td>
<td>Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial</td>
<td>NR</td>
</tr>
<tr>
<td>Harms</td>
<td>Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct</td>
<td>NA</td>
</tr>
<tr>
<td>Auditing</td>
<td>Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Ethics and dissemination

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research ethics approval</td>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
<td>11, line 5</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
<td>NR</td>
</tr>
<tr>
<td>Consent or assent</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
<td>9 line 1</td>
</tr>
<tr>
<td></td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
<td>NA</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
<td>11, line 12</td>
</tr>
<tr>
<td>Declaration of interests</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
<td>14, line 6</td>
</tr>
<tr>
<td>Access to data</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
<td>NR</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
<td>NA</td>
</tr>
</tbody>
</table>
Dissemination policy

31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

11, line 9

31b Authorship eligibility guidelines and any intended use of professional writers

NA

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

NR

Appendices

Informed consent materials

32 Model consent form and other related documentation given to participants and authorised surrogates

NR

Biological specimens

33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

LEGEND: NA= not applicable; NR= not reported.
**RECOvER** Checklist for reporting of enhanced recovery research

<table>
<thead>
<tr>
<th>Section</th>
<th>ItemNo</th>
<th>Recommendation</th>
<th>PAG.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Indicate that this is an enhanced recovery study in the title</td>
<td>1, line 1</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background</td>
<td>2</td>
<td>Explain the area of uncertainty that the study seeks to address</td>
<td>4, line 1</td>
</tr>
<tr>
<td>Guidelines</td>
<td>3</td>
<td>If a published set of enhanced recovery guidelines exists for this procedure, include a reference to the guidelines</td>
<td>4, line 9</td>
</tr>
<tr>
<td>Outcomes</td>
<td>4</td>
<td>Define the primary outcome and any key prespecified secondary outcomes for the study</td>
<td>8, line 9</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRB approval</td>
<td>5</td>
<td>Give the Institutional Review Board/Ethics Committee name and approval number. If permission was not required, reasons should be stated</td>
<td>11, line 5</td>
</tr>
<tr>
<td>Study design</td>
<td>6</td>
<td>Indicate what type of study is presented (randomized controlled trial, cohort, cross-sectional, etc.) The individual guidelines for the type of study should be followed (e.g., CONSORT for randomized controlled trial, STROBE for cohort studies, etc.)</td>
<td>5, line 15 SPIRIT in Supplemental materials</td>
</tr>
<tr>
<td>Setting</td>
<td>7</td>
<td>Describe whether this is a single or multicenter study, the type of practice (academic vs. community, tertiary vs. primary), and the providers (limited group or all providers on a service)</td>
<td>5, line 15</td>
</tr>
<tr>
<td>Timing</td>
<td>8</td>
<td>Describe periods of recruitment, time points at which outcomes assessed, and follow-up</td>
<td>NR</td>
</tr>
<tr>
<td>Participants</td>
<td>9</td>
<td>Define study inclusion and exclusion criteria</td>
<td>6, line 8</td>
</tr>
<tr>
<td>Enhanced</td>
<td>10</td>
<td>Describe when the enhanced recovery protocol was implemented relative to the study period</td>
<td>6, line 26</td>
</tr>
<tr>
<td>recovery protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Provide a flow diagram or table through the continuum of care detailing the enhanced recovery protocol including the following elements: (a) Preadmission patient education regarding the protocol (b) Preadmission screening and optimization as</td>
<td>NR</td>
</tr>
</tbody>
</table>
indicated for nutritional deficiency, frailty, anemia, HbA1c, tobacco cessation, and ethanol use.
(c) Fasting and carbohydrate loading guidelines (d) Preemptive analgesia (dose, route, timing) (e) Anti-emetic prophylaxis (dose, route, timing) (f) Intraoperative fluid management strategy (g) Types, doses, and routes of anesthetics administered (h) Patient warming strategy (i) Management of postoperative fluids (j) Postoperative analgesia and anti-emetic plans (k) Plan for opioid minimization (l) Drain and line management (m) Early mobilization strategy (n) Postoperative diet and bowel regimen management (o) Criteria for discharge (p) Tracking of post-discharge outcomes

Enhanced recovery auditing 12 Describe the audit system for compliance with the enhanced recovery protocol and how compliance data are measured 7, line 20

Outcomes 13 (a) Explain the criteria for assessing primary and secondary outcomes (b) Distinguish among clinical, functional, administrative, and quality of life outcome measures 8, line 9

PROs 14 If patient questionnaires are used, provide references to validation of these study instruments 8, line 23

Results

Patient population 15 Use a flow diagram to explain the derivation of the study population (a) Provide a Table I with the key demographic and clinical features of the study population (b) Indicate number of participants with missing data for each variable of interest NA

Enhanced recovery compliance 16 Provide a Table II with average compliance for each enhanced recovery protocol element and present a comparison of the variation in enhanced recovery compliance among the study groups NA

Correlations 17 Perform logistic regression to correlate the change in primary outcome with the study intervention NA

Discussion

Context 18 Explain what the study adds to the body of knowledge regarding the study intervention within the context of enhanced recovery after surgery care 12, line 12
<table>
<thead>
<tr>
<th>Limitations</th>
<th>19</th>
<th>Discuss the limitations of the study and how these might temper the findings</th>
<th>12, line 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>20</td>
<td>Document all sources of funding and potential conflicts of interest for the study authors</td>
<td>14, line 2</td>
</tr>
</tbody>
</table>

**LEGEND:** NA= not applicable; NR= not reported.